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Clinical effectiveness of treatment strategies for prosthetic joint infection following total ankle replacement: A systematic review and meta-analysis

Running title: Treatment strategies for infected ankle prostheses

Setor K. Kunutsor[1,2*], Matthew C. Barrett[3], Michael R. Whitehouse[1,2], Ashley W. Blom[1,2]

[1] National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK

[2]Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK

[3]Barts and The London School of Medicine and Dentistry, 4 Newark St, Whitechapel, London E1 2AT

Supplementary Material

Appendix 1	PRISMA checklist
Appendix 2	MOOSE checklist
Appendix 3	Literature search strategy

Appendix 1. PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	2
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	5
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	6
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	NA
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6; Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	7; Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	7; Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	7-8; Fig. 2; Appendix 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	7-8; Fig. 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	7
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	8-9
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as	11

Section/topic	Item No	Checklist item	Reported on page No
		supply of data) and role of funders for the systematic review	

Appendix 2. MOOSE checklist

Clinical effectiveness of treatment strategies for prosthetic joint infection following total ankle replacement: A systematic review and meta-analysis

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Prosthetic joint infection (PJI) after total ankle replacement (TAR) is a challenging complication, which often requires one- or two-stage revision surgery; implantation of a cement spacer; conversion to arthrodesis; or even amputation. The optimum treatment for ankle PJI is not well established. We conducted a systematic review and meta-analysis to compare the clinical effectiveness of various treatment strategies for infected ankle prostheses.
√	Hypothesis statement	It is uncertain which treatment strategies (long-term suppressive antibiotic treatment without surgical intervention; debridement, treatment with antibiotics and retention of the prosthesis (DAIR) with or without polyethylene exchange; one-stage revision surgery; two-stage revision surgery; prosthesis component removal and implantation of cement spacer; and arthrodesis) are clinically effective for the primary management of prosthetic joint infection following total ankle replacement (TAR).
√	Description of study outcomes	*Primary outcome* Re-infection (recurrent and new infections) *Secondary outcomes* (i) Pain (ii) Function - range of motion of the tibiotalar joint; orthopaedic Foot and Ankle Society score (AOFAS) (iii) Satisfaction (iv) Non-infection-related complications (such as implant failure, fracture, re-operation, non-union, loosening, haematoma, postoperative instability). (v) Conversion from one of the interventions to arthrodesis (v) Below-knee amputation
√	Type of exposure	(i) Long-term suppressive antibiotic treatment without surgical intervention (ii) Debridement, treatment with antibiotics and retention of the prosthesis (DAIR) with or without polyethylene exchange (iii) One-stage revision surgery (iv) Two-stage revision surgery (v) Prosthesis component removal and implantation of cement spacer (vi) Arthrodesis
√	Type of study designs used	Longitudinal studies (retrospective, prospective, or randomised controlled trials)
√	Study population	Patients in which the primary definitive treatment was one of the interventions above
Reporting of search strategy should include		
√	Qualifications of searchers	Setor Kunutsor, PhD; Matthew C. Barrett, BSc
√	Search strategy, including time period included in the synthesis and keywords	Time period: From inception to 29 November 2018. The detailed search strategy can be found in Appendix 3.
√	Databases and registries searched	MEDLINE, Embase, Web of Science, and Cochrane databases
√	Search software used, name and version, including special features	OvidSP was used to search Embase and MEDLINE EndNote used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language

√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	Not applicable
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We included only studies where populations were unselected
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the Methodological Index for Non-Randomised Studies (MINORS), a validated instrument which is designed for assessment of methodological quality of non-randomised studies in surgery
√	Assessment of heterogeneity	Not applicable
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analysis are detailed in the methods. We performed **fixed** effects meta-analysis with Stata 15.
√	Provision of appropriate tables and graphics	Table 1; Figures 1-2
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Not applicable due to limited number of studies
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses
Reporting of discussion should include		
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies. The systematic review is limited in scope, as it involves limited published data. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend evidence from a carefully designed randomised clinical trial or analysis of a joint registry database
√	Disclosure of funding source	In "Source of Funding" section

Appendix 3. Literature search strategy

Relevant studies, published before 10 December 2018 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, EMBASE, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), by hand searching of relevant journals and by correspondence with study investigators. The computer-based searches combined search terms related to ankle replacement, periprosthetic joint infection, and revision.

1 exp Prosthesis-Related Infections/ (10936)
2 prosthetic joint infection.mp. (1027)
3 exp INFECTION/ (746321)
4 exp Wound Infection/ (44161)
5 exp Surgical Wound Infection/ (34043)
6 surgical site infection.mp. (5775)
7 surgical infection.mp. (857)
8 exp SEPSIS/ (113818)
9 exp Ankle Joint/ (14535)
10 exp Arthroplasty, Replacement, Ankle/ (608)
11 total ankle replacement.mp. (624)
12 total ankle arthroplasty.mp. (555)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (761312)
14 9 or 10 or 11 or 12 (14910)
15 13 and 14 (476)
16 limit 15 to humans (469)

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Each part was specifically translated for searching the other databases – Embase and Cochrane Library